NCI GRANT sparks explosion of EARLY PHASE TRIALS

When Patricia LoRusso, DO, Professor of Medicine and Associate Director of Innovative Medicine came to Yale in 2014, she not only brought 25 years of experience in developing new drugs, but also a prestigious National Cancer Institute (NCI) grant that has launched more than a dozen new clinical trials at Smilow Cancer Hospital, with more coming.

The grant, called a UM1, is a 5-year grant that funds investigator-initiated clinical trials. UM1s are highly competitive—nationwide, the award is given to only 11 principal investigators and institutions, who can select other academic sites for collaborations in research and recruitment of patients. As Yale’s associate sites, Dr. LoRusso chose Wayne State, Vanderbilt, and the Universities of California at San Francisco and San Diego. In North America, 44 academic sites are under the umbrella of the 11 UM1s.

The grants support the NCI’s Experimental Therapeutics Clinical Trials Network (ETCTN), whose purpose is to encourage early phase clinical trials of innovative cancer therapies. Dr. LoRusso’s UM1 is certainly having that effect at Yale.

“There has been what I would call an explosion of investigator-initiated research here in the last two years,” she says, “and in large part it’s because the UM1 helps support those projects and also helps with mentoring junior investigators to bring these projects to fruition.”

A key aspect of the UM1/ETCTN is the NCI’s collaborative agreements with
Dr. LoRusso, the two projects approved under this mechanism may also be a formal protocol. If the project is approved, the NCI investigator can submit the idea to the NCI for review. If the NCI finds the idea is worth exploring, it requests the investigator can submit the idea to the NCI for review. If the NCI finds the idea is worth exploring, it requests the idea that includes testing a drug against a rare tumor, otherwise can be hard to get,” explains Dr. LoRusso. “It gives our researchers great access to drugs that funded researchers who need them for clinical trials. allows the NCI to provide these drugs to UM1- tumors,” says Dr. LoRusso, “or you might need special imaging or biopsies or a special assay. You can apply for a supplement to cover that. So far we’ve been very successful in obtaining supplements to help carry out the translational components of the clinical trials on the UM1.”

By the end of 2016, the NCI had approved 10 supplemental grants for Yale researchers, ranging in value from $150,000 to $1.3 million for biomarker research and also to help develop later stage, or Phase 2, clinical trials. Nearly all of the UM1 projects pair a senior investigator with a junior investigator, in keeping with the grant’s objective to junior investigators to bring these projects into the NCI’s pharmacopeia. With support from the UM1, says Dr. LoRusso, Dr. Karin’s idea is moving forward into a clinical trial. In hematology, Amir M. Zeidan, MBBS, Assistant Professor of Medicine, and Thomas Prebet, MD, PhD, Assistant Professor of Medicine, are working on UM1-funded concepts involving leukemia and lymphomas. Another project developed by Dr. LoRusso and Joseph M. McCahill, MD, a former medical oncology fellow who is now in private practice, is combining a PARP inhibitor with a checkpoint inhibitor against BRCA-mutated triple-negative breast cancer, again using drugs from the NCI pharmacopeia Michael Cecchini, MD, a second-year Clinical Fellow, illustrates how Dr. LoRusso and the UM1 invests in early phase clinical trials. Dr. Cecchini is interested in gastrointestinal malignancies. In their early phase clinical trial, the two collaborated on a clinical trial that Dr. LoRusso, the two clinical scientists batted around ideas to explore. They noticed that a recent paper had mentioned a subset of gastric cancer patients who had a minimal signature characteristic of homologous DNA repair. This signature has been linked to several cancers, including pancreatic, breast, and ovarian, and has been combined with PARP inhibitors, which kill cells by hindering them from repairing their damaged DNA. But definitive DNA repair drugs hadn’t previously been associated with gastric cancer, so Dr. Cecchini and Dr. LoRusso saw an opportunity to test PARP inhibitors against it. They also speculated that adding an angiogenesis inhibitor that suppressed the development of new blood vessels in the tumor could boost the PARP inhibitor’s effectiveness. This combination has shown promise against other cancers, especially ovarian.

The two submitted the idea to the NCI in spring of 2016 and were asked to submit a full protocol. The project was approved under the UM1 at the end of the year, and Dr. Cecchini says they expect to start enrolling patients in their clinical trial by mid-2017. The University of California at San Francisco will collaborate on the minimal several EUTIC sites will help to enroll patients. Asked how important the UM1 grant has been to him as a junior investigator, Dr. Cecchini says, “It’s incredible. Any type of clinical trial is really challenging, and I’ve learned so much. We’ve integrated with the NCI but also potentially working with 44 other centers, and we also have our collaborators at UCSF. As a junior investigator, I’m getting to interact with faculty across the country. Without the UM1, none of that would be possible. I haven’t heard of many other fellows getting such a unique opportunity. I feel really fortunate, and also fortunate that I have our collaborators at UCSF. As a junior investigator, I’m getting to interact with faculty across the country. Without the UM1, none of that would be possible. I haven’t heard of many other fellows getting such a unique opportunity. I feel really fortunate, and also fortunate that Dr. LoRusso is available as a mentor for me.”

Dr. LoRusso is in the third year of her five-year UM1, and she hopes that Yale and their UM1 consortium will be able to renew the grant again—the has successfully re-composed for the UM1’s early therapeutics grants for about 20 years. She is hopeful that this explosion of investigator-initiated research at Yale sparked by the UM1 will continue for years to come.

pharmaceutical companies, whose new therapies

"We only ask a pivotal question in the lab and come up with results, we’re asking if that science means improved outcomes for patients in the clinic."